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ORIGINAL ARTICLE

Analysis of mortality rates for gallbladder cancer across the world

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Abstract
Aim. Ethnic background and geographical location are important when measuring the incidence of gallbladder carcinoma leading to variable mortality rates across the world. *Method.* Age standardized mortality rates [ASR(W)] were extracted separately for males and females from a database maintained by the International Agency for Research on Cancer for 50 countries across the world (Europe 32; the Americas 8; and Asia 10) for the period 1992–2002 and log-linear regression was performed to analyse trends in the last decade. *Result.* In the period 1992–2002, declining trends in mortality for both sexes were observed in Germany, Sweden, Japan, USA, and Hungary ($p<0.001$), and in France, Canada, United Kingdom, The Netherlands, and Hong Kong ($p<0.01$). Austria, Czechoslovakia, Slovenia, Denmark, Spain, and Israel exhibited decreasing mortality trends more significant in women ($p<0.01$) than in men ($p<0.05$). Decreasing female mortality trends were seen in Finland, Italy, and Portugal ($p<0.01$) and in Georgia, Luxembourg, and Belgium ($p<0.05$). Iceland, Costa Rica, and Korea were the only countries with an increase in male mortality ($p<0.05$). *Conclusions.* Overall, there was a decline in ASR(W) for gallbladder cancer. Better diagnostic modalities resulting in appropriate staging of gallbladder/biliary cancers, as well as changes in the ICD classification and perhaps increased awareness, may have contributed to these trends.

Key Words: *Age standardized mortality, gallbladder cancer, trends*

Introduction

Primary carcinoma of the gallbladder is the most common biliary tract tumor and the sixth most common cancer affecting the gastrointestinal tract [1,2]. The majority of cases are diagnosed in the advanced stages, leading to extremely poor prognosis. The prognosis is mainly dependent on histological subtype, grade, and stage of the tumor at the time of presentation. The overall mean survival rate for patients with gallbladder cancer (GBC) is 6 months, with a 5-year survival rate of 5% [1].

GBC has a female predilection, especially women >65 years of age [3]. The commonest association of GBC is with gallstones, i.e. larger stones contributing to increased risk [4,5]. The other risk factors for developing GBC include chronic infection of the biliary tract, in particular due to *Salmonella typhi*, chemical exposure, cigarette smoking, high parity, post-menopausal state, diet, and obesity [3,6–8].

A unique feature of GBC is that it exhibits marked geographic and ethnic variation [6–11]. We evaluated the possible changes in mortality trends in GBC in view of the relatively standardized diagnostic modalities over the last 10 years (1992–2002).

Methods

The database maintained by the International Agency for Research on Cancer (IARC) – the CANCER Mondial Statistical Information System (http://www.dep.iarc.fr/) – was accessed and age standardized mortality rate (world) [ASR(W)] due to GBC was extracted separately for males and females for the period 1992–2002 for 50 countries across the world. The database contains cancer mortality statistics by country extracted from the World Health Organization (WHO) databank. The original data have been converted and/or recorded to a common system and the information on quality of data, such as presence of histological ascertainment, extent of population coverage, and percentage of death certificate only registration, is not available. Of the 115 WHO member states that have some method of death registration,

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only 29 have an "ideal" civil registration system, while countries such as China and India have only a "sample" registration system [12]. Data were thus available from 32 countries in Europe (*West Europe*: Belgium, France, Germany, Ireland, Luxembourg, The Netherlands, Switzerland, and the United Kingdom; *East Europe*: Estonia, Latvia, Lithuania, Moldova, Poland, and Romania; *North Europe*: Denmark, Finland, Iceland, Norway, and Sweden; *South Europe*: Albania, Croatia, Greece, Italy, Macedonia, Malta, Portugal, Slovenia, and Spain; *Central Europe*: Austria, Czechoslovakia, Hungary, and Slovakia), 10 countries in Asia (*South East Asia*: Hong Kong, Philippines, Singapore, and Thailand; *North East Asia*: Japan, Korea; *Middle East*: Georgia, Israel, Kuwait, and Kyrgyzstan), and 8 countries across the Americas (*North America*: Canada and the United States of America; *South America*: Colombia, Costa Rica, Ecuador, Mexico, Uruguay, and Venezuela). Log-linear regression was used to analyse trends for the period 1992–2002. Correlation coefficients were calculated, with a positive value indicating an increasing trend and a negative value a falling trend; $p < 0.05$ was considered significant.

Results

Europe

The ASR(W) due to GBC in the period 1992–2002 for both males and females has been static across most countries in Europe. Hungary and Czechoslovakia in Central Europe were exceptions, with mortality rates highest in 1992 for both sexes: males (6.5 and 6.4, respectively) and females (12 and 9.2, respectively), declining to 4.6 and 4.5, respectively, in the case of males, and 4.8 and 4.6, respectively, in the case of females in 2002. The mortality rates were high in Germany, Sweden, and Slovenia in 1992 [male range (3.4–4.8), female range (5.3–6.8)] with subsequent decrease in 2002 [male range (1.7–2.0), female range (2.2–3.1)]. The decreasing trends (both sexes) were found to be highly significant in Hungary, Germany, and Sweden ($p < 0.001$), while the decline in trend was more significant in females than in males in Czechoslovakia and Austria (females $p < 0.01$; males $p < 0.05$). Declining trends in mortality for both sexes ($p < 0.01$) were also seen in the UK, The Netherlands, and France, while in Denmark, Slovenia, and Spain the downward trend was more significant in women ($p < 0.001$) compared to men ($p < 0.05$). Decreasing trends solely in women were noted in Finland, Italy, Portugal ($p < 0.01$), and in Georgia, Luxembourg, and Belgium ($p < 0.05$).

Iceland was the only country in Europe where a significant increase in mortality trends ($p < 0.05$) was seen in the case of males (0.75 in 1992 to 2 in 2002) due to GBC, while mortality trends in the case of women did not attain significance.

Asia

The decline in ASR(W) in both males and females due to GBC in the period 1992–2002 was seen in Japan, Hong Kong, and Israel. Mortality trends decreased in Japan and Hong Kong ($p < 0.01$), while in Israel the downward trend was more significant in women ($p < 0.01$) compared to men ($p < 0.05$).Korea was the only country in Asia to register increasing mortality rates for both males (6 in 1995 to 8 in 2001) and females (3.2 in 1995 to 5 in 2001), and this upward trend was more significant in women ($p < 0.01$) than in men ($p < 0.05$) (data unavailable prior to 1995).

North America

The decreasing mortality rates due to GBC in Canada and the USA in the period 1992–2002 were replicated in both sexes, while the mortality trends were more significant in Canadian women ($p < 0.001$) than in Canadian men ($p < 0.01$).

South America

The analysis of age standardized mortality rates in the period 1992–2002 was limited to Columbia, Costa Rica, and Ecuador, with no data available after 1997. Mortality rates remained static for women across these countries, with a decrease in male mortality in Ecuador and Columbia, barring Costa Rica, where male mortality increased from 1.6 in 1992 to 2.2 in 1997, this upward trend being significant ($p < 0.05$).

Discussion

Our analysis suggests that, in the Western world, mortality due to GBC fell in the last decade of the second millennium. However, this is in stark contrast to the increase seen in Korea, Costa Rica, and Iceland. The first possibility is the variation in quality of data available in international registries, along with the absence of incidence data, population size, and demographics [13,14]. In addition, the extent of histological verification is not available, nor is information on diagnostic and treatment modalities used for the tumors of the biliary tract. Few data were available for the South American and Asian countries, where the incidence of GBC is known to be high. We have assumed the effects in all countries to be equivalent regardless of population size and this can be seen in Table I, as there is variation in the total number of deaths for each country. However, the fact that we used ASR(W), a standard comparative tool, can account for some of the variation. Secondly, the observed variations could reflect a consolidation of the diagnostic modalities used [15,16]. The use of high resolution CT scans/ERCP/MRCP/EUS/laparoscopy is now the norm in the West, leading to

Table I. Significant trends in the mortality of gallbladder cancer, 1992–2002.

Region	Country	Males: Deaths (range)	Males: Coefficient	Males: 95% CI	Males: *p*-value	Females: Deaths (range)	Females: Coefficient	Females: 95% CI	Females: *p*-value
Northern Europe	Denmark	36–53	−0.034	(−0.076, 0.008)	0.1	59–109	−0.077	(−0.091, −0.062)	<0.001
	Finland	44–72			NS	119–174	−0.052	(−0.076, −0.028)	0.001
	Iceland	1 to 3	0.095	(0.005, 0.185)	0.04	0–10			NS
	Norway	40–54			NS	55–91	−0.031	(−0.069, 0.006)	0.09
	Sweden	181–296	−0.064	(−0.086, −0.043)	<0.001	343–681	−0.087	(−0.115, −0.059)	<0.001
Southern Europe	Albania	1 to 10			NS	1 to 6			NS
	Croatia	51–77			NS	105–162			NS
	Greece	79–157			NS	119–190			NS
	Italy	1386–1645			NS	2876–3086	−0.017	(−0.024, −0.009)	0.001
	Macedonia	9 to 21			NS	17–36			NS
	Malta	0–5			NS	0–6	−0.112	(−0.245, 0.022)	0.09
	Portugal	118–180			NS	161–277	−0.054	(−0.084, −0.023)	0.003
	Slovenia	33–56	−0.05	(−0.087, −0.013)	0.01	60–138	−0.108	(−0.132, −0.084)	<0.001
	Spain	437–662	−0.042	(−0.074, −0.009)	0.02	895–1523	−0.078	(−0.108, −0.047)	<0.001
Western Europe	Belgium	97–198	−0.116	(−0.244, 0.012)	0.07	172–346	−0.12	(−0.240, 0.004)	0.05
	France	519–850	−0.064	(−0.093, −0.035)	0.001	831–1690	−0.082	(−0.118, −0.046)	0.001
	Germany	1282–2070	−0.075	(−0.095, −0.056)	<0.001	2825–6172	−0.109	(−0.139, 0.079)	<0.001
	Ireland	17–39			NS	38–77			NS
	Luxembourg	0–6			NS	2 to 9	−0.133	(−0.263, −0.003)	0.05
	Netherlands	102–215	−0.087	(−0.130, −0.044)	0.001	184–490	−0.123	(−0.154, −0.091)	<0.001
	Switzerland	71–85			NS	174–187	0.043	(−0.021, 0.107)	0.07
	UK	198–458	−0.078	(−0.103, −0.054)	<0.001	392–889	−0.067	(−0.100, −0.034)	0.001
Central Europe	Austria	125–231	−0.042	(−0.077, −0.008	0.02	232–646	−0.065	(−0.104, −0.027)	0.004
	Czech	268–436	−0.043	(−0.071, 0.016)	0.01	549–1004	−0.065	(−0.093, −0.037)	0.001
	Hungary	243–490	−0.075	(−0.010, −0.046)	<0.001	577–1436	−0.116	(−0.150, −0.081)	<0.001
	Slovakia	78–102				191–249			
Middle East Asia	Israel	0–59	−0.16	(−0.256, −0.052)	0.01	0–118	−0.139	(−0.214, −0.064)	0.003
	Kuwait	0–5				2 to 5	−0.071	(−0.155, 0.013)	0.09
North Asia	Georgia	2 to 7			NS	5 to 17	−0.384	(−0.667, −0.109)	0.03
	Russia	NA			NS	NA			
	Kyrgyzstan	8 to 12			NS	15 to 26			
North East Asia	Japan	6189–7885	−0.043	(−0.060, −0.026)	<0.001	7557–11616	−0.078	(−0.108, −0.048)	<0.001
	Korea	983–1599	0.025	(0.002, 0.049)	0.04	768–1413	0.049	(0.025, 0.072)	0.002
South East Asia	Hong Kong	51–86	−0.074	(−0.101, −0.046)	<0.001	70–96	−0.047	(−0.078, −0.015)	0.008
	Philippines	42–62			NS	41–63			NS
	Singapore	17–38			NS	21–58			NS
	Thailand	NA	−0.114	(−0.260, 0.032)	0.1	NA			NS
North America	Canada	188–326	−0.068	(−0.099, −0.038)	0.001	294–562	−0.09	(−0.118, −0.063)	<0.001
	USA	1288–2008	−0.072	(−0.094, −0.051)	<0.001	4077–2120	−0.09	(−0.012. −0.060)	<0.001

Table I (*Continued*)

Region	Country	Males				Females			
		Deaths (range)	Coefficient	95% CI	*p*-value	Deaths (range)	Coefficient	95% CI	*p*-value
South America	Colombia	NA			NS	NA			NS
	Costa Rica	NA	0.051	(0.009, 0.094)	0.03	NA			NS
	Ecuador	NA			NS	NA			NS
	Mexico	NA			NP	NA			NP
	Uruguay	NA			NP	NA			NP
	Venezuela	NA			NP	NA			NP

NS = not significant; NP = not performed; CI = confidence interval.

improved clinical diagnosis of gallstone disease (a known risk factor) as well as better separation of GBCs from bile duct cancers. The incorporation of these modalities has also led to: 1) improved diagnosis and standardization of treatment of gallstone disease using laparoscopic cholecystectomy, which probably reduces the risk of development of GBC, contributing to the decreasing trend. This hypothesis will need to be tested in population-based studies; 2) a corresponding increase in the diagnosis of hilar cholangiocarcinomas, a common differential diagnosis of GBCs causing biliary obstruction: these are classified as intrahepatic cholangiocarcinomas by the International Classification of Diseases-10 (ICD-10). This increase has been reported recently [15,17]; and 3) the reclassification of hepatobiliary tumors that would previously have been described as cholangiocarcinomas, hepatocellular carcinomas, or unclassified [15,17].

This revision of ICD-10 in 1992 may have further contributed to the declining trend because, for the first time, GBC was classified separately from other cancers affecting the biliary tract [18].

Lastly, we have to consider that the changes we have observed are real. However, further in-depth analysis is required if definitive trends are to be ascertained, and for which larger datasets would be required over longer periods of time (more than 20 years) along with incidence data and demographics. These data are currently unavailable for the majority of countries.

Randi et al., in reviewing the incidence of GBC worldwide, found that the highest incidence (data post mid-1990s) was in women from Delhi, India (21.5/100,000), South Karachi, Pakistan (13.8/100,000), and Quito, Ecuador (12.9/100,000) [11]. Among men, the highest incidence was in Busan, Korea (8/100,000), and Delhi, India (7.5/100,000). High incidences of GBC (women: 8–11/100,000, men: 3–8/100,000) in cancer registries were found in Korea, Japan, countries of eastern Europe (Slovakia, Poland, Czech Republic, and Yugoslavia), while low incidence rates were observed in most registries across northern Europe barring Sweden and North America. The female/male ratio also varied, with the highest ratio in Pakistan, Columbia, and Spain. The sex ratio in the vast majority of countries was between 2 and 3, while the incidence in males and females was virtually equal in Korea, Japan, and some parts of China. Unfortunately, data for these countries were sparse in our study.

This variation can also be seen among ethnic groups, where Hispanic white women in California and New Mexico showed a 3 to 5-fold higher incidence (8–5.4/100,000) than non-Hispanic women in the same areas. American Indians too exhibited a high incidence of GBC. This ethnic variation is less prominent among men, barring American Indians. Various inferences can be drawn from these differences, especially with the worldwide distribution of gallstones, which has a strong positive correlation with the incidence of GBC [9,10]. A high prevalence of gallstones was reported in the regions of South America and parts of Eastern and Central Europe [11]. Thus, the prevention of gallstones may important in decreasing the incidence of GBC, especially in high-risk areas.

Through this preliminary analysis, we have attempted to explain the variations in GBC mortality in different parts of the world. Insights that may be gained from this study include the changed use of various diagnostic modalities and that may explain the differences seen. The epidemiologies of gallbladder and related cancers deserve a more in-depth study when more data become available.

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References

[1] Levy AD, Murakata LA, Rohrmann CA, Jr. Gallbladder carcinoma: radiologic–pathologic correlation. Radiographics 2001;21:295–314; questionnaire, 549–55.

[2] Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43–66.

[3] Eduardo C, Lazcano-Ponce JFM, Muñoz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. CA: a Cancer Journal for Clinicians 2001;51:349–64.

[4] Lowenfels AB, Walker AM, Althaus DP, Townsend G, Domellof L. Gallstone growth, size, and risk of gallbladder cancer: an interracial study. Int J Epidemiol 1989;18:50–4.

[5] Diehl AK. Gallstone size and the risk of gallbladder cancer. J Am Med Assoc 1983;250:2323–6.

[6] Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348: 1625–38.

[7] Wood R, Fraser LA, Brewster DH, Garden OJ. Epidemiology of gallbladder cancer and trends in cholecystectomy rates in Scotland, 1968–1998. Eur J Cancer 2003;39:2080–6.

[8] Pandey M, Shukla VK. Lifestyle, parity, menstrual and reproductive factors and risk of gallbladder cancer. Eur J Cancer Prev 2003;12:269–72.

[9] Zatonski W, La Vecchia C, Levi F, Negri E, Lucchini F. Descriptive epidemiology of gall-bladder cancer in Europe. J Cancer Res Clin Oncol 1993;119:165–71.

[10] Zatonski WA, Lowenfels AB, Boyle P, Maisonneuve P, Bueno de Mesquita HB, Ghadirian P, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. J Natl Cancer Inst 1997;89:1132–8.

[11] Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 2006;118:1591–602.

[12] Baiden F, Bawah A, Biai S, Binka F, Boerma T, Byass P, et al. Setting international standards for verbal autopsy. Bull World Health Org 2007;85:570–1.

[13] Newnham A, Quinn MJ, Babb P, Kang JY, Majeed A. Trends in the subsite and morphology of oesophageal and gastric cancer in England and Wales 1971–1998. Aliment Pharmacol Ther 2003;17:665–76.

[14] Ghadirian P, Lynch HT, Krewski D. Epidemiology of pancreatic cancer: an overview. Cancer Detect Prev 2003;27:87–93.

[15] Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33:1353–7.

[16] Taylor-Robinson SD, Toledano MB, Arora S, Keegan TJ, Hargreaves S, Beck A, et al. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968–1998. Gut 2001;48:816–20.

[17] Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? J Hepatol. 2004;40:472–7.

[18] WHO. International classification of diseases (ICD-10). Geneva: WHO. 1992.